FAMILIAL ICTERUS GRAVIS OF THE NEW-BORN AND ITS TREATMENT

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IT is to Abt that the credit is due for first calling the attention of the American profession to this rare form of disease in 1917. Pfannenstiehl, however, gave the first detailed description of familial icterus of new-born children. He described two fatal cases and collected the scattered reports in the literature in 1908. More recently Klemperer, in 1924, gave an admirable detailed description of the pathological findings of three cases, two of which were quite typical of this condition.

It was my fortune to be called by Dr. Murray, of Parkdale, to see the case which is the subject of this paper a few hours after the baby was born on December 18, 1924. The baby was a perfectly healthy looking, fine specimen of male child weighing between eight and nine pounds. The family history, however, was so remarkable that one was prepared for trouble. As the father informed me, they had had six boys born previously all apparently as healthy and strong at birth as this baby. They all, however, had developed jaundice within the first twenty-four hours, and the condition had become progressively worse until death occurred in from three to eleven days. They had only one child living, a girl who was the second child born to the family. She had become jaundiced as the others and although it was felt that she was going the same road as they had gone, she had managed to live although deeply jaundiced until one year old and weighing at this age only what she had weighed at birth. After a year the jaundice gradually disappeared and she grew very rapidly so that she is now at twelve years a very big girl for her age but suffering with chorea. There was absolutely no history of jaundice in the family on either the paternal or maternal side and both parents were perfectly healthy. There was no specific history. There had been no miscarriages. The baby was a well developed male child, two hours old, and so far as one could find, perfectly healthy and at this time with no sign of jaundice. On the second day, the father stated that he could see jaundice beginning to appear on the tip of the nose but as it was evening and only artificial light could be used I could not see it myself. On the next day, however, the baby being then forty-eight hours old, he was distinctly jaundiced. The liver was not enlarged and as the jaundice was no more intense than ordinary icterus neonatorum, I found it difficult to be sure that it was a more serious condition. During this time the baby was taking the breast vigorously every four hours and taking large quantities of water between nursings as instructed on the first day. The stool was still meconium. On the third day, the jaundice had become much more intense so that the skin was a deep orange colour. The pupils were equal, the scleroties had a distinctly yellow tinge and the baby tended to be drowsy. The tongue was furred, the gums and throat clear. The hard palate showed a yellow tinge. The abdomen was flaccid and the liver just palpable at the costal margin. The spleen was not enlarged and the umbilicus was perfectly clean. The respiratory and circulatory systems were normal. The *blood examination* showed as follows: Red blood cells 4,200,000; white blood cells 9,000; hæmoglobin 85 per cent.; polymorphonuclears 68 per cent; lymphocytes 32 per cent. The blood film showed no abnormality of the red or white cells. Unfortunately, although it had been asked for, by a misunderstanding the bleeding and clotting time was not done. *Fragility test,* point of minimal resistance 0.45 saline, point of maximum resistance 0.25 saline, which are within normal limits. *Van Der Bergh's test,* direct test negative, indirect test strongly positive. This together with a normal fragility test would seem to indicate damage to the liver cells. The stools which were losing the nature of meconium looked as though they contained bile and the Gmelin's test for bile was strongly positive.

The urine also contained bile. The blood culture was sterile and the temperature had not been above normal since birth.

It was quite certain that we were dealing with a case of familial icterus gravis but on looking up the literature upon all the reported cases one could find very few helpful suggestions for treatment. Klemperer who described the pathology so admirably suggested that one should try to protect the liver against destruction by sustaining its glycogen reserve. He concluded that the beneficial results of glucose transfusion in mushroom poisoning, (Treupel and Rehorn) and in the toxæmia of pregnancy (Titus and Givens) which aim towards the same point, suggested the same therapy in cases of severe jaundice in the new-born. His pathological findings in the two cases which seemed clinically from their history to belong to this group, showed in the first case a diffuse not a focal necrosis and destruction of the liver cells, most conspicuous but not limited to the central areas of the lobules. Fatty changes were present in this case but only to a moderate extent. He pointed out the similarity to the pathological findings in acute yellow atrophy. However, he could not be absolutely certain that some of the changes might not be due to an umbilical infection in his first case, as there was some slight clinical evidence of a navel infection, although the anatomic and histologic examinations furnished no confirmatory evidence of this. His second case showed more extensive fatty changes with bile duct proliferation and reparation of liver cells in the periphery. His third case he concluded himself was not a case of familial icterus gravis, but a case of icterus neonatorum. In none of his cases were there any signs of obliteration of the bile ducts. These two cases together with the two cases which Abt had reported were the only ones which I was able to find in the American literature.

Abt states that the cause is unknown, that the disease has nothing in common with Buhl's or Winkel's disease, and that there is nothing to prove that familial icterus gravis is due to a septic process. He further states that there is no history of birth injury nor does it seem to be due to any toxæmia of pregnancy. He draws attention to the fact that most of these children are strong, robust and mature at birth but in a sense they appear to be physically defective and very soon become incapacitated to carry on extra-uterine existence and that it is possible that the liver fails in the performance of its extra-uterine function. After a good clinical description he concludes by stating that the disease is of unknown origin, is nearly always fatal, and recommends no treatment.

Knopfelmacher is inclined to think that some septic process is involved to explain this group of cases. He considers that the habitual occurrence of the disease in the same family was not sufficient argument against the consideration of sepsis and is of the opinion that a chronic infection of the vaginal portion of the birth canal of the mother might serve as the origin of infection in successive cases.

Rolleston thinks that the toxæmia of pregnancy might be a cause. He found that out of twenty-five family groups which he had collected—that was in fifteen out of one hundred and thirty cases of newly born infants with familial icterus gravis, the mothers had recurrent jaundice during their pregnancies. It was interesting to note that all of these cases went to full term. He points out that the disease appears to be less likely to attack the first and second born than the later infants in the families affected. He gathered from the literature that in fourteen out of twenty-five families collected the first-born escaped, and in several families the first-born was slightly jaundiced and was the only one to recover. He stated that there was no evidence that syphilis plays any part and no good reason for regarding infection as a cause. In the cases which he had collected there were thirty-one males and thirty-one females so that it would not appear that sex was a factor.

Discussion.—Regarding Rolleston's suggestion that the disease is due to toxæmia of pregnancy, there is nothing to suggest it in this family. The mother was never better in her life than she was during this pregnancy. She had no signs of any jaundice and has never had any. She had no headaches and the only trouble she had was some cramps in her legs. Also in this case there was no sign of sepsis or infection of any kind. The mother had no sisters but her brothers had normal children. The father's brothers and sisters also had normal children. There was no evidence of syphilis. It would look as if, from the results of the treatment to

be described later, and the course of the case, that the condition was due to some unknown toxin circulating in the blood and possibly absorbed from the gastro-intestinal tract.

Clinical features.—Briefly reviewing the clinical features of familial icterus gravis we have an afebrile form of jaundice which is peculiar to certain families and tends to occur in successive pregnancies. The children when born appear to be quite normal but die a few days after birth as the result of a grave and progressive icterus. As a rule there is no hereditary influence. Nothing of a similar nature is discovered in the family of the father or mother. The disease begins on the first or second day of life and rapidly increases in severity. The stools may be slightly loose and contain mucus. They are not acholic. The urine usually contains bile pigment. Sometimes the liver and spleen are enlarged. If treatment is not instituted the jaundice becomes progressively more intense, the baby becomes drowsy, and frequently signs of meningeal irritation develop with characteristic crying and whining (all the cases in this family which were allowed to progress developed these latter symptoms). Death follows in a few days from collapse.

Diagnosis. — Simple, physiological or idiopathic jaundice has been estimated to occur in 33 per cent. and upwards of all birth. The jaundice begins within the first two days and appears earlier than in the cases of grave infective jaundice. There are no symptoms although sleepiness is mentioned by Langmead. It is differentiated from this rare condition of familial icterus gravis by the family history and the course of the case. No treatment is necessary.

Congenital obliteration of the bile ducts is accompanied by hepatic and splenic enlargement and practically always proves fatal within eight months. It is therefore relatively chronic as compared with familial icterus gravis. The first case of familial icterus gravis in a family would be difficult to distinguish from this, although hepatic and splenic enlargement with acholic stools would be in favour of gross obstruction.

In severe infective forms of jaundice, such as those due to umbilical, cutaneous or intestinal infection, the jaundice comes on about the fifth day of life, later than in familial icterus gravis, and is accompanied by signs of grave septicæmia, high fever and hæmorrhages especially from the umbilicus or alimentary canal. Winckel's disease and Buhl's disease are manifestations of this septicæmia of the newly born, in which the infection probably enters from the intestine.

Acholuric family jaundice runs a mild course. There is an hereditary history and the spleen is enlarged. It is recognized by the characteristic fragility of the red blood corpuscles.

Congenital syphilis does not often cause jaundice. It usually comes on early and is accompanied by other signs of the disease.

Sometimes in hæmorrhagic disease of the new born jaundice is present, but in these cases the bleeding is the outstanding symptom which will serve to differentiate it.

Prognosis.—The prognosis has always been given as bad. Out of one hundred and thirty cases collected by Rolleston, one hundred or 77 per cent. proved fatal.

Treatment.—As stated earlier, in going over the literature, one could not find many suggestions for the treatment of these cases. Rolleston suggested prophylactic treatment of the mother on the hypothesis that the condition was due to a fœtal toxæmia of maternal origin. It was too late to do anything of that nature and one could find no evidence of any toxæmia of pregnancy in this case. He also suggested small doses of calomel for the infant but the child was becoming so rapidly worse that one did not feel that calomel would have any material effect. Since in this case there was no evidence of infection or sepsis it seemed as though the condition must be due to some toxin circulating in the blood which was destroying the liver cells, and as both the parents and I felt that if something drastic was not done at once the child was certainly going to die as the six other previous male babies had done, it was decided to do an exsanguination transfusion after the technique brought out and perfected by the late Dr. Bruce Robertson, in the hope of removing a sufficient amount of toxin to prevent the progress of the disease. The baby was in Group II Jansky. Dr. J. L. MacDonald, of the Hospital for Sick Children exsanguinated three hundred cc. of blood from the anterior fontanelle at the same time transfusing 335 cc. of blood into the internal saphenous vein at the left ankle. The transfusion of blood was commenced after 20 cc. of blood had been removed

and the transfusion and exsanguination went on synchronously until the required quantity had been used, and we ended by giving the baby 35 cc. more than had been removed. In addition 60 cc. of 5 per cent. glucose solution were given. The donor was a healthy male not belonging to the family. By the following morning the jaundice was much less intense. It continued to fade so that by the fourth day it had entirely disappeared and the baby seemed much better. When three weeks old there was a slight return of jaundice. Preceding this he had been constipated. This slight return of jaundice had entirely disappeared four days after it was first noted and when the constipation had been corrected. He has had no return of the jaundice since and is gaining and developing at five and a half months as any normal baby—weight seventeen pounds. He is still on the breast so that it would hardly seem as if the mother's milk were a factor. I should like to point out that transfusion without exsanguination had been done to Klemperer's three cases but apparently without much benefit.

Conclusions

1.—It would appear as though familial icterus gravis of the newly born were due to a toxin of some unknown origin operating upon the liver in certain rare families.

2.—The return of the jaundice in the case cited following constipation suggests the possibility of absorption from the intestine being a factor in these cases.

3.—Early exsanguination transfusion before the liver cells have been too extensively damaged would seem to cure the condition if a sufficiently large exsanguination transfusion be done.

4.—The possibility of beneficial effects from the administration of glucose should be considered as an auxiliary.

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A Typhoid Carrier.—The patient whose case is cited by C. B. Sylvester and A. W. Sylvester, Portland, Me., was a typhoid carrier for twenty-nine years. It is to be noted, as evidence of his personal neatness and cleanliness, that for nine years he worked in a hotel without knowledge of typhoid resulting. The intimate associations of family life were promptly and dramatically productive of disease. The case is a valuable testimonial to the localization of *B. typhosus* in the gallbladder. It is also made evident by an investigation of submucous tissue in the gallbladder that any treatment short of removal must be futile.—*Jour. A. M. A.*, July 11, 1925.